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(21) International Application Number: PCT/SE92/00631 (22) International Filing Date: 14 September 1992 (14.09.92) (30) Priority data: 9103395-1 18 November 1991 (18.11.91) SE (71) Applicant (for all designated States except US): GAMBRO AB [SE/SE]; Box 10101, S-220 10 Lund (SE). (72) Inventors; and (75) Inventors/Applicants (for US only) : JÖNSSON, Sven [SE/SE]; Poppelvägen 8, S-245 44 Staffanstorp (SE). KJELLSTRAND, Per [SE/SE]; Ekvägen 25, S-240 17 Södra Sandby (SE). MARTINSON, Evi [SE/SE]; Blåmesvägen 40, S-240 17 Södra Sandby (SE). WIESLANDER, Anders [SE/SE]; Våpplingevägen 17 A, S-222 38 Lund (SE). SVENSSON, Eva [SE/SE]; Janne Nilssons väg 5, S-242 32 Malmö (SE). ANDREN, Anders [SE/SE]; Malmgatan 16, S-211 32 Malmö (SE).		(74) Agent: BOBERG, Nils, Gunnar, Erik; Gambro AB, Patent Department, Box 10101, S-220 10 Lund (SE). (81) Designated States: JP, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, SE). Published <i>With international search report.</i> <i>In English translation (filed in Swedish).</i>
(54) Title: SYSTEM EMPLOYING A STERILE MEDICAL SOLUTION CONTAINING GLUCOSE OR GLUCOSE-LIKE COMPOUNDS AND A SOLUTION INTENDED FOR SAID SYSTEM		
(57) Abstract <p>System employing a sterile medical solution containing glucose or glucose-like compounds, for example nutritional solutions or solutions for peritoneal dialysis, whereby the majority of the solution is packed in a first package (A), whilst the glucose or the glucose-like compounds are separately packed in a second package (B), whereafter the two packages are heat sterilized. The invention is characterized in that the content of the glucose or glucose-like compounds in the second package (B) is maintained above 10 % by weight, suitable above 20 % by weight and preferably in the order of 40 % by weight in order to reduce or totally eliminate the breakdown of said compounds. The invention also relates to a solution intended for the system according to the invention. The solution is characterized in that, after sterilization, mixing and diluting to 1,5 % glucose content, it has an absorbency caused by breakdown products from glucose at 228 nm less than 0,35 and preferably in the order of 0,20 or lower. Alternatively, the solution according to the invention is defined in that, after sterilization, mixing and dilution to 1,5 % glucose content, it has an ICG-value caused by breakdown products from glucose less than 50 %, preferably less than 30 %.</p>		

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TITLE

SYSTEM EMPLOYING A STERILE MEDICAL SOLUTION CONTAINING GLUCOSE OR GLUCOSE-LIKE COMPOUNDS AND A SOLUTION INTENDED FOR SAID SYSTEM.

TECHNICAL FIELD

The present invention relates to a system employing a sterile medical solution comprising glucose or glucose-like compounds, for example nutritional solutions or solutions for peritoneal dialysis, whereby the majority of the solution is packed in a package whilst the glucose or the glucose-like compounds are packed separately in a second package, whereafter the two packages are heat sterilized. By the expression glucose-like compounds is meant for example glucose polymers.

BACKGROUND OF THE INVENTION

It is known to pack a CAPD-solution in a two chamber package from, for example, the article "In Vitro Testing of a Potentially Biocompatible Continuous Ambulatory Peritoneal Dialysis Fluid" by N Topey et al, in Nephrol Dial Transplant (1991) 6:574-581.

The same, or at least a similar, two chamber package having essentially the same inventors is described in international patent application no. WO 91/08008. From e.g. Example 1 of this document it is apparent that the two parts of the package are intended to contain essentially the same quantity of solution. Thus, when the article refers to a larger and smaller package respectively, this is assumed to mean that even in this case the two packages will contain the same quantity of solution, though with the one package being made larger so as to be able to serve as a mixing chamber.

It is known from, for example, the article "Toxity of peritoneal dialysis fluids on cultured fibroblasts L-929" by Anders Wieslander et al, in Kidney International, Vol 40 (1991) pp 77-79, that heat sterilized CAPD-solutions can contain harmful components which can depend on the decomposition of certain compounds, for example glucose, during the sterilization.

It is known from, for example, US Patent 4 369 779 and 4 753 697 to achieve a sterile coupling between two tubes in various ways, which can be joined to two separate packages.

DESCRIPTION OF THE INVENTION

The present invention can be said to be a development of the above mentioned teachings and relates to a system making use of a sterile medical solution comprising glucose or glucose-like compounds, for example nutritional solutions or solutions for peritoneal dialysis, whereby the majority of the solution is packed in a package whilst the glucose or the glucose-like compounds are separately packed in a second package, whereafter the two packages are heat sterilized.

The system according to the invention is characterized in that the content of the glucose or glucose-like compounds in the second package is maintained above 10% by weight, suitably above 20% by weight, and preferably in the order of 40% by weight. In this manner the breakdown of the packaged product is reduced. At the same time the risk of breakdown is reduced since the product which is sensitive to breakdown need not be in contact with all the compounds in the final solution during heat sterilization.

A further advantage with the invention is the possibility to achieve a final neutral solution with a pH between 6,5 and 7,5. Preferably, a pH of 7,0 is hereby achieved. Here it should be stressed that as far as we are aware no such neutral solutions for PD-dialysis are presently commercially available on the market.

In practice, it has been shown to be possible to make use of a sterilizing temperature between 110°C and 150°C and sterilizing times between 180 minutes and 10 minutes from the commencement of heating to cooling to room temperature. At the same time the time interval for the maximum heating should hereby be kept as short as possible, though sufficiently long, of course, to meet the requirements imposed by the authorities so that sufficient death rate of bacteria and spores is obtained.

One possibility is that the two packages are manufactured separately and each one provided with a connection piece or connection tube. Preferably, both packages are completely sealed and each one provided with a connection piece or connection tube made from a heat sealable material and sealed at its extremity with a welded seal, which is intended to be removed or opened under maintained sterility for connection of the two packages together and mixing of their contents. Equipment and procedure for such a connection is described in the above mentioned American patents which are therefore included in the present description. The invention does however also include other known or future sterile connections, for example such as those which are nowadays used for CAPD. An advantage with this embodiment is that the smaller package can be separately heat sterilized at a high temperature for a short period with a short heating period and a short cooling period.

Alternatively, the second package containing said glucose or glucose-like compounds can form a minor part of a double package, for example a double bag, the other part of which forms the first package. The two parts can then be made to communicate with each other for mixing of the contents. The first package should thereby have such volume that in addition to its original contents, it can also accommodate the contents of the second package. An advantage with this embodiment is that an openable connection conduit can be arranged between the two packages already during their manufacture. The heating up time for the smaller package will however be somewhat dependent on the heating up time of the larger package. Even in this

case, however, it is desirable that the sterilisation temperature is kept high and the heating up time short.

Suitably, the contents of the smaller glucose-containing package are maintained at a low pH during sterilisation, preferably in the order of 3,5. At the same time, the contents of the two packages during sterilisation should be maintained with such respective pH-values that the final resultant product after mixing is substantially neutral, i.e. with a pH between, for example, 6,5 and 7,5, preferably about 7,0.

The invention further relates to a solution intended for a system of the above defined type. This solution is characterized in that, after sterilization, mixing and diluting to 1,5% glucose content, it has an absorbency caused by breakdown products from glucose at 228 nm of less than 0,35 and preferably 0,20 or lower.

Where the solution according to the invention is intended for peritoneal dialysis the system, according to the invention can comprise a smaller package containing 20-500 ml, preferably approximately 65-75 ml glucose with a pH of approximately 3-6, preferably approximately 3,5 and a glucose content of 10-70%, preferably approximately 40%, as well as a larger package containing the remaining compounds, for example Na-lactate 9g, NaCl 10,8g, CaCl_2 380 mg and MgCl_2 102 mg, with a pH adjusted to a desired value between 6 and 8,5, and preferably distilled water in a quantity in the order of 2 litres, for example 1935-1925 ml.

The solution according to the invention can also be defined in such a manner that, after sterilization, mixing and diluting to 1,5% glucose content, it has an ICG-value (Inhibition of Cell Growth tested on cultured fibroblasts L-929) caused by breakdown products from glucose of less than 50%, preferably less than 30%. The reason for this definition is, as can be seen from Fig. 4, that the degree of inhibited cell growth bears a close relation to the UV-absorbency at 228 nm. It must however be taken into consideration that the solution should not contain compounds other than glucose or glucose-like compounds with absorbency at 228 nm. Should the solution contain other such compounds, then the absorbency will be

affected. With knowledge of the included compounds it can however be calculated how much of the absorbency is dependent on breakdown products from glucose.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 shows a double package intended to be used in connection with the system according to the invention.

Fig. 2 shows an alternative in the form of two separate bags.

Fig. 3 illustrates the relationship between the glucose content and the ICG-value after heat sterilising of glucose dissolved in pure water.

Fig. 4 shows the relationship between the ICG-value and the UV-absorbency at 228 nm after heat sterilizing solutions having different glucose content in pure water.

Fig. 5 show the absorbency at 228 nm after heat sterilizing solutions with different glucose contents in pure water.

Fig. 6 shows in the form of a bar chart a comparison between the ICG-values after heat sterilizing water solutions with 1,5% and 40% glucose respectively.

Fig. 7 illustrates in the same manner a comparison between the absorbency at 228 nm after heat sterilizing water solutions with 1,5% and 40% glucose respectively.

BEST MODE OF CARRYING OUT THE INVENTION

From the above mentioned article by Anders Wieslander et al it is apparent that existing commercial glucose solutions inhibit the growth of cultured fibroblasts. This implies that the glucose solutions contain one or more substances which are toxic in the biological system.

From a comparison of, for example, sterile filtered solutions and heat sterilized solutions with essentially the same contents, it appears that the toxic effect depends on the substances formed in connection with the heat sterilization or the subsequence storage. Here it should be noted that the authorities in many countries require a sterilization after packaging of the product. In principle this is not possible with sterile filtered solutions.

From, for example, the graph in Fig. 4 it can be seen that the toxic effect (percentage inhibited growth), and thereby also the quantity of toxic substances, is related to the absorbency at 228 nm. This implies that a glucose solution with low absorbency is, from a toxicological view, probably better than a solution with high absorbency at 228 nm.

The aim has been to provide a glucose solution with a considerably lower toxic effect on the biological system compared with sterile glucose solutions commercially available until now. By low toxicity is meant that, accordingly to the invention, a glucose solution diluted to a glucose content of 1,5% may not inhibit cell growth of cultured fibroblasts L-929 through breakdown products (tested according to the above mentioned article by Anders Wieslander et al which is hereby included in the present description) by more than 50% and preferably by not more than 30%.

Two alternative bag systems are shown in Figs. 1 and 2 which can form the above mentioned packages. In Fig. 1 a double bag is shown consisting of a larger part A and a smaller part B which are separated by a weld or other seal C. The ends of the double package are sealed in a similar manner by welds or other means D, E respectively. The weld C can be entirely break-openable. Alternatively, the two bag parts A and B can be connected already during manufacture by means of a tube F containing a suitable breakable seal, for example a conventional breakpin.

The alternative shown in Fig. 2 consists of a separate larger bag A and a similarly separate smaller bag B. The two bags are provided with connection pieces or connection conduits denoted by G and H respectively. Each of these connection pieces can be provided with sterile connecting halves for sterile connection. In the shown example it is intended that they be terminated with an end sealing weld I, J respectively. A sterile connection can thus be achieved in the manner described by way of example in said above mentioned American patents. The contents of these are therefore included in the present description.

The alternative according to Fig. 2 enjoys the advantage that the bag A can be heat sterilized in a conventional manner at the same time that a particularly quick heating and cooling of the bag B can be achieved if it is manufactured from two plastic sheets laid one on top of the other which are joined to each other along the periphery and which have dimensions such that the layer of glucose solution can be maintained relatively thin during the heat sterilization. By way of example, a bag containing 75 ml of glucose solution can have the dimensions 10 cm by 10 cm.

The larger bag A can, if used in peritoneal dialysis, contain a salt solution with the contents Na-lactate 9g, NaCl 10,8g, CaCl_2 380 mg and MgCl_2 102 mg (the composition can be varied somewhat). The pH should be adjusted to the desired value between 7 and 9. Finally, the bag preferably contains distilled water in a quantity in the order of 2 litres, for example 1925-1935 ml. The heat sterilization is envisaged to take place in a conventional manner in an autoclave with suitably adapted time and temperatures.

The small bag B can contain glucose concentrate, for example 20-500 ml, preferably 65-75 ml, 10-70% glucose, preferably 40%. The pH-value should lie between 3 and 6, preferably about 3,5. The sterilization may be effected in a autoclave at a temperature between 110°C and 145°C, suitably above 120°C and preferably at 130°C. With the embodiment according to Fig.1 the bag part B is of course sterilized at the same time as the bag part A. With the embodiment according to Fig. 2, the bag B is however suitably sterilized separately so that the necessary sterilizing temperature can be quickly reached and thereafter obtain a quick cooling.

During the trials F_0 equal to 40 was sought, though in practice this value varied somewhat. By F_0 is meant the time in minutes which the solution should need to be maintained at 121°C in order to become sterile in accordance with that which is demanded by supervising authorities. F_0 equal to 10 implies therefore that the product must be maintained at 121°C for 10 minutes in order to achieve sterility.

The following table presents the results of a number of experimental tests. In line 1 a sterile-filtered, i.e. non-heat sterilized, complete solution for PD containing 1,5% glucose was tested. The three following lines show the results with heat sterilization with differing F_0 of a complete PD-solution in which the glucose was added at the beginning. These solutions also included 1,5% glucose.

The last three lines give the results of tests on complete mixing with which a glucose solution was heat sterilized separately so that first after sterilizing it could be mixed with remaining compounds included in the PD-solution. The glucose concentration was hereby maintained during the sterilizing at about 40%. After the mixing together, this was reduced to 1,5% in agreement with the concentration of remaining solutions in the comparative tests.

From the table it can further be seen that with help of the invention the concentration of acetaldehyde can be kept low by separately sterilising the glucose solution. Acetaldehyde is a typical breakdown product from glucose and the amount of this product should be kept below 1,0 ppm, suitably below 0,1 ppm and preferably in the order of 0,01-0,001 ppm.

In Fig. 4 the relationship is shown between the absorbency at 228 nm and the ICG-values after heat sterilising of a number of glucose solutions in pure water. The graph shows that the condition for an acceptable product can either be defined by means of a low absorbency value or low ICG-value.

Fig. 5 shows the absorbency at 228 nm after heat-sterilising for a number of glucose solutions in pure water. The higher the glucose concentration is maintained, the lower the absorbency and thus also the ICG-value becomes. In practice, however, the glucose concentration should not be maintained above about 40%. In addition, particularly at low temperatures there is a risk of crystal-formation.

Finally, Figs. 6 and 7 show respectively a comparison between the absorbency values at 228 nm for a sterilized water solution with 1,5% glucose in complete condition and a corresponding 1,5% solution in which the glucose was sterilized separately at a concentration of 40%.

The invention has been described in the above particularly in connection with peritoneal dialysis, more particularly CAPD. It will however be apparent that the invention can also be suitable in connection with other sterile solutions containing glucose or glucose-like compounds, for example polymers of glucose. By way of example the invention can be suitable in connection with sterilization of nutritional solutions containing glucose or glucose-like compounds which otherwise will be problematic in terms of breakdown products in connection with heat sterilization.

Table

The toxicity and breakdown products in PD-solutions after heat sterilizing. The PD-solutions were sterilized either as a conventional bag or double bag with glucose concentrate. All values refer to finally mixed end products.

Test solution	F ₀	<u>Absorbency</u>		<u>Acet-</u> <u>alde-</u> <u>hyde</u>	<u>Form-</u> <u>aldehyde</u>	<u>Cyto-</u> <u>toxi-</u> <u>city</u>
		228 nm	284 nm	ppm	ppm	%
Sterile- filtered	0	0.295	0.011	0.005	<0.005	16
Complete	10	0.467	0.053	4.0	0.005	44
Complete	20	0.666	0.110	8.8	0.005	73
Complete	30	0.765	0.150	11.6	0.2	83
Glucose conc	10	0.404	0.074	0.005	<0.005	21
Glucose conc	20	0.419	0.112	0.005	<0.005	25
Glucose conc	30	0.414	0.158	0.005	<0.005	27

CLAIMS

1. System employing a sterile medical solution containing glucose or glucose-like compounds, for example nutritional solutions or solutions for peritoneal dialysis, whereby the majority of the solution is packed in a first package (A), whilst the glucose or the glucose-like compounds are separately packed in a second package (B), whereafter the two packages are heat sterilized, characterized in that the content of the glucose or glucose-like compounds in the second package (B) is maintained above 10% by weight, suitably above 20% by weight and preferably in the order of 40% by weight in order to reduce or totally eliminate the breakdown of said compounds.

2. System according to claim 1, characterized in that said second package (B) is separately heat sterilized to permit heating to a high temperature in a short time, whereby the breakdown of the packaged products is further reduced or totally avoided.

3. System according to claim 1 or 2, characterized in that the separately packed compound or compounds in the second package (B) are sterilized at a temperature between 110°C and 150°C, preferably above 120°C.

4. System according to claim 3, characterized in that heating takes place during a time interval of 180 to 10 minutes from commencement of heating to cooling to room temperature.

5. System according to any one of claims 2 to 4, characterized in that the two packages are totally sealed and each one provided with a connection piece or connection tube (G, H resp) made from a heat sealable material and closed at its extremity with a sealing weld (I, J resp), which is intended to be removed or opened during maintained sterility for joining of the two packages (A and B) and mixing of their contents.

6. System according to claim 1, characterized in that the second package (B) containing said glucose or glucose-like compounds forms a minor part of a double package, for example a double bag, the other part of which forms the first package (A), and in that the two parts can be made to communicate with each other for mixing of the contents.

7. System according to any one of the preceding claims, characterized in that the first package (A) has such volume that in addition to its original contents, it can also accommodate the contents of the second package (B).

8. System according to any one of the preceding claims, characterized in that the contents of the second package are maintained at a low pH during sterilisation, preferably in the order of 3,5.

9. System according to any one of the preceding claims, characterized in that the contents of the two packages during sterilisation are maintained with such respective pH-values that the final resultant product after mixing is substantially neutral, i.e. with a pH between, for example, 6,5 and 7,5, preferably about 7,0.

10. Solution intended for a system according to any one of claims 1 to 9, characterized in that after sterilization, mixing and diluting to 1,5% glucose content, it has an absorbency caused by breakdown products from glucose at 228 nm less than 0,35 and preferably in the order of 0,20 or lower.

11. Solution according to claim 10, intended for peritoneal dialysis, characterized in that it consists of a smaller package containing 20 to 500 ml, preferably approximately 65-75 ml glucose with a pH of approximately 3-6, preferably approximately 3,5, and a glucose content of 10-70%, preferably around 40%, and a larger package containing remaining included compounds, for example Na-lactate 9g, NaCl 10,8g, CaCl_2 380 mg and MgCl_2 102 mg, with a pH adjusted to a desired value between 6 and 8,5 and preferably distilled water in a quantity in the order of 2 litres, for example 1935-1925 ml.

12. Solution intended for a system according to any one of claims 1 to 9, characterized in that after sterilization, mixing and dilution to 1,5% glucose content, it has an ICG-value (Inhibition of Cell Growth tested on cultured fibroblasts L-929) caused by breakdown products from glucose less than 50%, preferably less than 30%.

13. Solution intended for a system according to any one of claims 1 to 9, characterized in that it contains a quantity of acetaldehyde with a ppm-value less than 1,0, suitably less than 0,1 and preferably in the order of 0,01-0,001.

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Fig.1

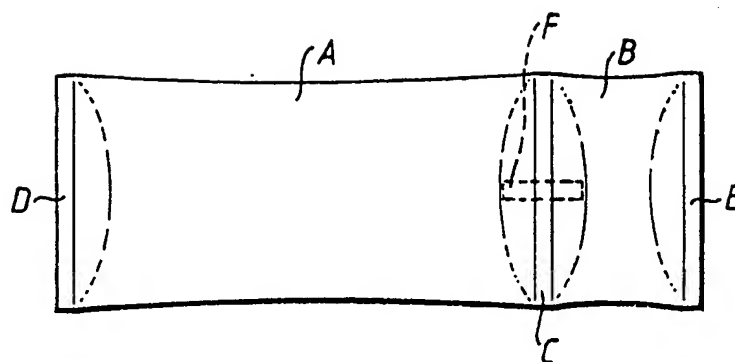
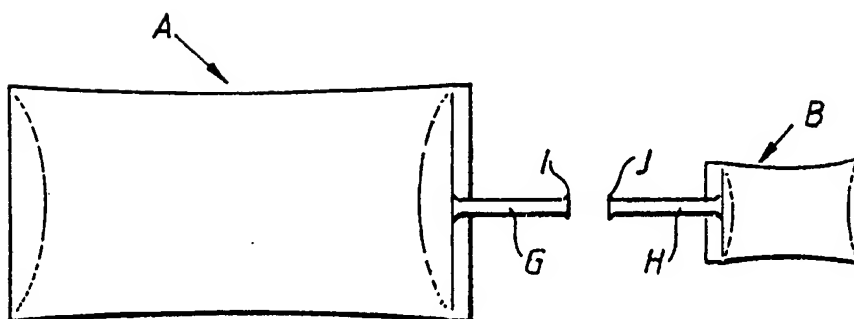


Fig. 2



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Fig. 3

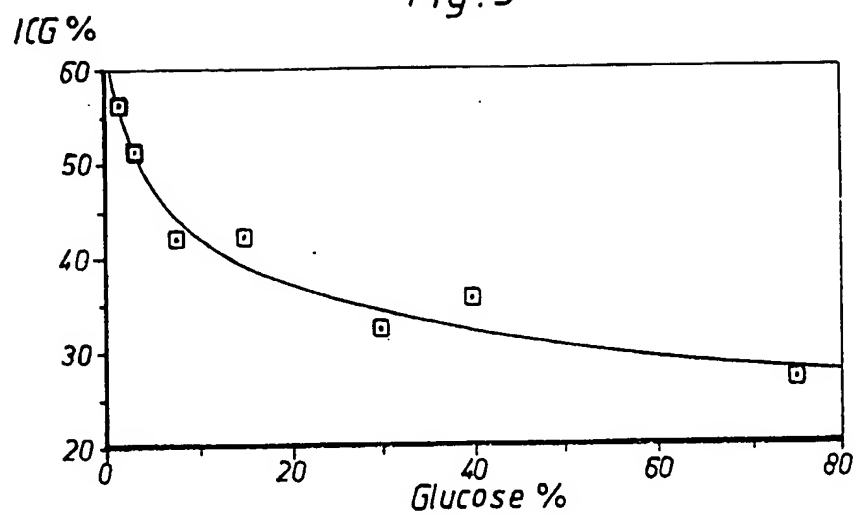


Fig. 4

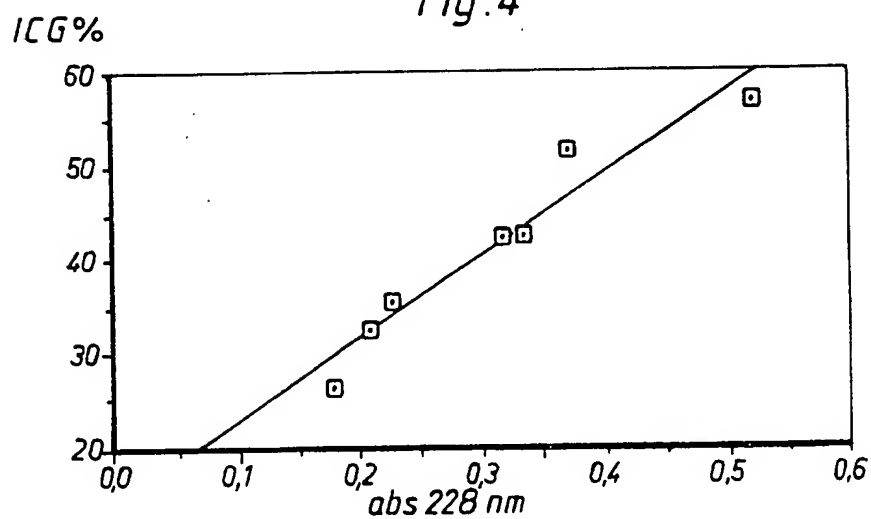
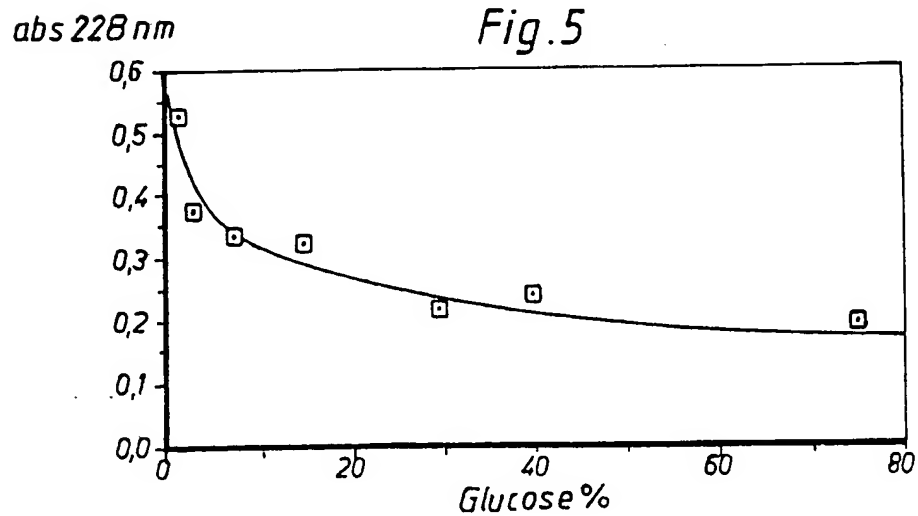


Fig. 5



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Fig. 6

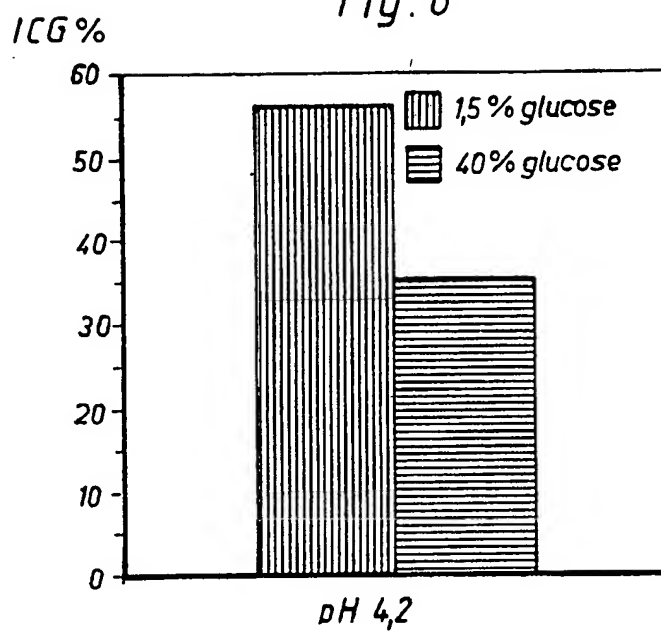
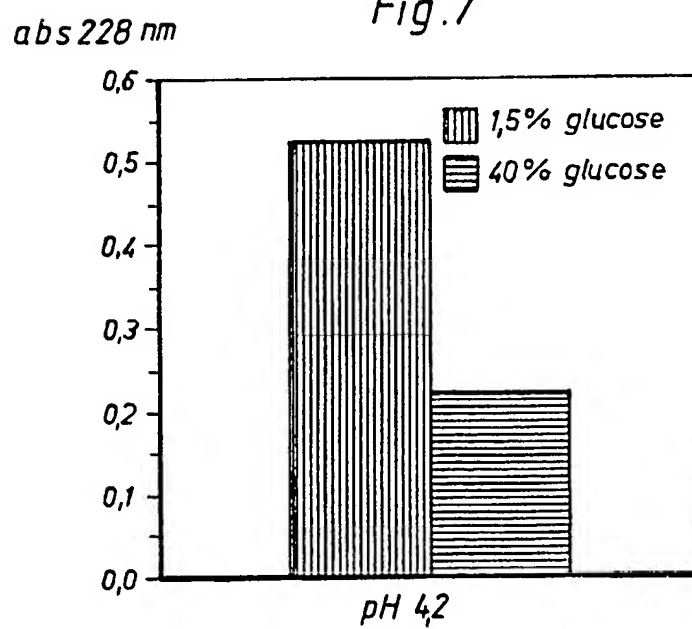


Fig. 7



INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 92/00631

A. CLASSIFICATION OF SUBJECT MATTER

IPC5: A61M 1/14, A61K 37/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC5: A61J, A61K, A61L, A61M

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO, A2, 9108008 (BAXTER INTERNATIONAL INC), 13 June 1991 (13.06.91), page 6, line 17 - line 24; page 8; page 9, ex. 1	1-4,8-11
Y	--	5-7
Y	US, A, 4368729 (LUC M. DOSSIN), 18 January 1983 (18.01.83), figures 1-4, abstract	5-7
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☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

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International application No.
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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Kidney International, Volume 40, 1991, Anders P. Wieslander et al, "Toxicity of peritoneal dialysis fluids on cultured fibroblasts", page 77 - page 79, table 1	10
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A	US, A, 4753697 (JOHN B. SHAPOSKA ET AL), 28 June 1988 (28.06.88)	1-11
A	---	1-11
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INTERNATIONAL SEARCH REPORT
Information on patent family members

29/01/93

International application No.
PCT/SE 92/00631

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US-A- 4753697	28/06/88	NONE	
US-A- 4369779	25/01/83	AU-B- 542643 CA-A- 1174419 CA-A- 1174712 EP-A,B- 0044204 SE-T3- 0044204	28/02/85 18/09/84 18/09/84 20/01/82